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22 NOV 2010

IN THE MATTER OF  
US PATENT APPLICATION NO. 10/563,234  
IN THE NAME OF  
CHELSEA AND WESTMINSTER NHS TRUST

**STATUTORY DECLARATION**

I, Dr Hazem El-Refaey of 63 Waver Tree Road, London SW2 3SL, do hereby solemnly and sincerely declare as follows:-

1. This Declaration is made in replacement of my previous Declaration in the matter of US Patent Application No. 10/563,234 signed on 19 October 2010.
2. I am a consultant Obstetrician and Gynaecologist at the Chelsea and Westminster Hospital and I was a Lead Clinician for the Hospital's Early Pregnancy Care Unit. After graduating from Cairo University, I have worked for several years as a doctor in the UK. I obtained my MD degree with merits from Aberdeen University and specialist training in Obstetrics & Gynaecology at University College of London. I am involved with the research of new treatments and the modification of established treatments in the field of Obstetrics and Gynaecology. I confirm that the information set out herein is taken from my own personal knowledge or from relevant records of documents relating thereto to which I have full access.
3. I am the inventor of US Patent Application No. 10/563,234, European patent registration number EP1641470, and PCT patent application number PCT/GB2004/002867.
4. I am also a named author on 27 research papers published in medical or scientific journals in the field of Obstetrics and Gynaecology, including studies into the use of azithromycin and misoprostol.
5. Based upon my aforementioned experience, I believe that one of ordinary skill in the art at the time at the invention was made, being provided with US Patent Application No. 10/563,234 and the Example of the invention contained therein, would understand that a synergistic effect could be achieved by administering vaginally a therapeutically effective amount of 250 milligrams to about 1000 milligrams of azithromycin and 50 micrograms to about 1000 micrograms of misoprostol, thereby leading to the improved treatment of pelvic tissue infection and the reduction of surgical trauma resulting from a gynaecological operation.
6. Moreover, I believe that one of ordinary skill in the art at the time the invention was made would have been able to ascertain a trend in the

exemplified data of US Patent Application No. 10/563,234 that would allow one of ordinary skill in the art to reasonably extend the probative value thereof and thus expect that a synergistic effect is achieved throughout the entire of the aforementioned range of amounts of azithromycin and misoprostol. Namely, I believe that one of ordinary skill in the art at the time the invention was made would understand that a synergistic effect will result from administering vaginally: 250 milligrams of azithromycin and 50 micrograms of misoprostol; 250 milligrams of azithromycin and 1000 micrograms of misoprostol; 1000 milligrams of azithromycin and 50 micrograms of misoprostol; 1000 milligrams of azithromycin and 1000 micrograms of misoprostol; and all amounts of azithromycin and misoprostol between.

7. The aforementioned synergistic effect is believed to result from the collagenolytic properties of misoprostol enhancing the delivery of azithromycin to vaginal tissue. Specifically, the collagenolytic properties of misoprostol help to break apart collagen at the site of administration and allows for azithromycin to be more easily absorbed into the vaginal tissue. This synergistic effect between azithromycin and misoprostol thereby results in the high levels of azithromycin found in the target tissue compared to administration of azithromycin alone. Consequently, the vaginal administration of azithromycin and misoprostol provides improved treatment of pelvic tissue infection and the reduction of surgical trauma resulting from a gynaecological operation.
8. In this connection, I enclose herewith as ANNEX 1 an article from the European Journal of Obstetrics & Gynecology and Reproductive Biology volume 123 (2005) pages 62-66 "Light-induced fluorescence of the human cervix decreases after prostaglandin application for induction of labor at term", as evidence in support of the collagenolytic properties of misoprostol when administered vaginally in an amount of 50 micrograms.

9. In this connection, I enclose herewith as ANNEX 2 an article from the European Journal of Obstetrics & Gynecology and Reproductive Biology Vol. 67, No. 5, page 633-636 "Cervical Collagen: An Important Regulator of Cervical Function in Term Labor" as evidence in support of the collagenolytic properties of prostaglandins when administered vaginally in an amount of 500 micrograms.

AND I MAKE this solemn Declaration conscientiously believing the same to be true.

Declared at.....*London*.....

this.....*22*.....day of.....*November*.....2010

*H T*  
.....*CEFA*.....